In This Issue

Cell

Glial Nurr1 Is Neuroprotective

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Nurr1 is a transcription factor that is essential for the generation and maintenance of dopaminergic neurons in the brain, and mutations in *Nurr1* are associated with familial Parkinson's disease. Saijo et al. now show that Nurr1 is expressed in microglia and astroctyes, where it inhibits expression of genes encoding proinflammatory neurotoxic mediators by recruiting a transcriptional repression complex that shuts off NF-κB. Loss of Nurr1 results in exaggerated inflammatory responses in microglia that are further amplified by astrocytes, leading to the production of toxic factors that can induce neuronal death. These studies suggest that Nurr1 protects against Parkinson's disease by limiting the production of neurotoxic mediators.

Acetylation Takes Huntington to the Dumpster

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Accumulation and aggregation of disease-causing proteins is a hallmark of several neurodegenerative disorders. Clearance of accumulated proteins via endogenous mechanisms, for instance autophagy, may represent a therapeutic avenue for disease amelioration. However, current approaches to modulating autophagy are nonspecific. Using the example of Huntington's disease, Jeong et al. now show that posttranslational modification of the disease variant of huntingtin by acetylation promotes autophagic clearance of the mutant protein. Enhanced clearance rescues cells from the toxic effects of protein accumulation and can prevent neurodegeneration.These studies identify acetylation as a mechanism for selective targeting of proteins for degradation.

A New Twist on Burning Fat

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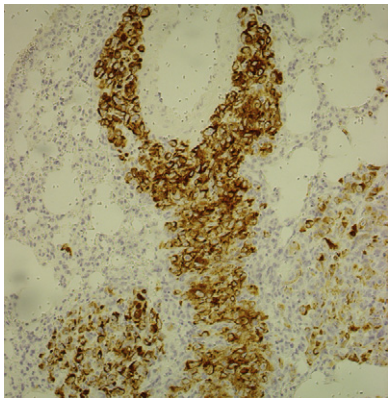
Brown fat is specialized to produce heat, a process that is controlled by the transcriptional coactivator PGC-1α. Pan et al. show that the transcription factor twist-1 is selectively expressed in adipose tissue and is a key negative regulator of PGC-1α. The presence or absence of twist-1 directly affects metabolism, sensitizing mice to either weight gain or obesity resistance, respectively. Interestingly, PPARδ, a known mediator of PGC-1α action, also regulates twist-1 expression, suggesting a negative feedback regulatory mechanism. These findings provide molecular insights into how brown fat metabolism is regulated and coordinated to achieve energy homeostasis.

p63 at the Hub of Metastasis



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The genes and signals controlling metastasis are poorly understood. Adorno et al. show here that three common contributors to human cancers, oncogenic Ras, mutant-p53, and aberrant TGFβ signaling, all so far independently implicated in metastasis, actually conspire toward the same goal, the inactivation of p63. p63 is an important regulator of normal stem cells but prevents cancer stem cells from becoming metastatic. The authors unveil new genes downstream of this pathway that may be used as a prognostic tool for breast cancer.

Keeping VSG under RAP

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Several microbial pathogens, including *Trypanosoma brucei*, evade the host immune defenses by periodically changing their surface antigen, a phenomenon termed antigenic variation. In *T. brucei*, it is crucial that a single type of variant surface glycoprotein (VSG) is expressed at any time while keeping the remaining VSG genes silent. Now Yang et al. discover a trypanosomal telomere gene, tbRAP1, to be essential for keeping subtelomeric VSGs fully silenced. The findings demonstrate that telomeres are critical for this important virulence mechanism.

Polycomb Hangs on during Replication

PAGE 110

Heritable gene regulatory events are believed to be central to cellular differentiation and development and may involve heritable changes in chromatin. How specific chromatin structures could be inherited through DNA replication is not known. PRC1-class Polycomb group protein complexes are essential for development, as they epigenetically silence genes. Using a cell-free system, Francis et al. find that PRC1 complexes can be retained through a round of DNA replication. The results suggest that the transfer of chromatin-modifying proteins through DNA replication may be a mechanism for heritable gene regulation.

DNA, Paper, Scissors

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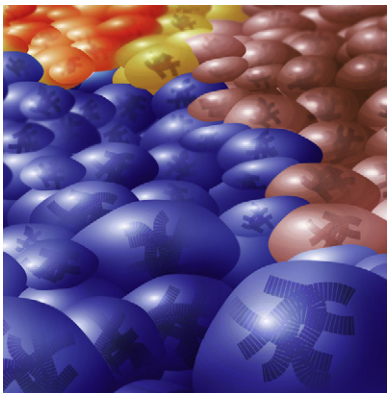
Sister chromatids are held together in metaphase by cohesins, which are cleaved by the protease separase at anaphase. Regulation of separase is critical for avoiding premature sister separation and aneuploidy. Sun et al. now demonstrate that chromosomal DNA is required to enable human separase to cleave cohesin. The authors provide evidence that DNA bridges the interaction between separase and cohesin and suggest that this mechanism explains why only chromosome-associated cohesins are cleaved during anaphase, and soluble cohesins are left intact.

A Plenitude of Prion Domains



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Prions are proteins that convert between structurally and functionally distinct states, one or more of which is transmissible. During a comprehensive screen for prions in the *Saccharomyces cerevisiae* genome, Alberti et al. uncovered several prion domains capable of driving phenotype-switching behavior. The sequences of the identified prion domains also reveal important amino acid biases for amyloid-based prion formation. The authors show that the environmentally responsive transcription factor Mot3p harbors one of the identified prion domains and is able to promote cell wall heterogeneity within a population of cells. These findings support the concept that yeast prions can change the genotype-phenotype landscape in a heritable manner with potentially wide-ranging consequences for survival and evolution.

The Chains We Need for Degradation

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Ligation of polyubiquitin chains to protein substrates is known to mediate a number of cellular processes, such as proteosomal degradation of the substrate. K48-linked chains have been thought to play a prominent role in mediating proteosomal degradation while the roles of chains linked through lysines K6, K11, K27, K29, or K33 are not as well understood. By a quantitative proteomics analysis, Xu et al. show that these unconventional linkages are abundant in vivo in yeast and may target proteins for degradation. K11-linked chains are shown to play an important role in endoplasmic reticulum-associated degradation. Thus, the study expands our understanding of the specific functions among differently linked ubiquitin chains.

Making a Mesh of PSD

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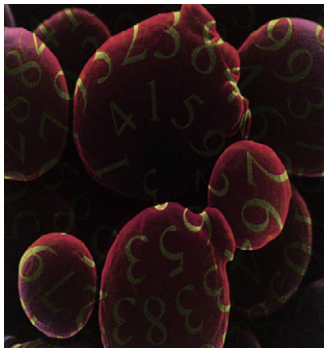
The postsynaptic density (PSD) forms on the cytoplasmic surface of postsynaptic membranes and includes signaling molecules, scaffolding proteins, cytoskeletal proteins, and their regulators. In this issue, Hayashi et al. show that two abundant PSD proteins, Homer and Shank, can interact to form an extended mesh-like assembly. Structural analysis of Homer reveals that its tetramerization enables it to crosslink Shank to form a network. Such a network may serve as an assembly platform for other PSD proteins at excitatory synapses and may therefore provide the structural framework for the postsynaptic density.

Setting a Standard in Systems Biology



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Gene regulatory networks are the underlying circuitry of the cell enabling it to perform all the necessary functions needed to sustain life. Recent efforts in systems and synthetic biology aim at understanding and predicting the behavior of these networks particularly through modeling and reverse-engineering approaches. However, it is difficult to assess the usefulness and predictive ability of modeling and reverse-engineering without a ''gold standard'' for comparison. Working in *Saccharomyces cerevisiae*, Cantone et al. built a synthetic, five gene network for in vivo benchmarking. The complex behaviors of the system make it a challenging test case for new algorithms or engineering approaches and for network modeling.